AD_____

Award Number: W81XWH-11-C-0033

TITLE: Phase III Clinical Trials: D-Methionine to Reduce Noise-Induced Hearing Loss

PRINCIPAL INVESTIGATOR: Kathleen C.M. Campbell, PhD.

CONTRACTING ORGANIZATION: Southern Illinois University School of Medicine, Springfield Illinois, 62794

REPORT DATE: March 2014

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
March 2014	Annual	01March2013-28February2014

4. TITLE AND SUBTITLE
Phase III Clinical Trials: D-Methionine to Reduce Noise-Induced Hearing Loss

5b. GRANT NUMBER
W81XWH-11-C-0033

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Kathleen C.M. Campbell, PhD.

E-Mail: kcampbell@siumed.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Southern Illinois University School of Medicine
Springfield, Illinois

8. PERFORMING ORGANIZATION REPORT

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Hearing loss can render a soldier less able to detect and identify the enemy, less able to understand commands, particularly in background noise typical on the battlefield, and may permanently reduce quality of life. Currently, no FDA approved pharmacological prevention exists for noise-induced hearing loss (NIHL). We have documented in animal studies that administration of D-methionine (D-met) can reduce or prevent NIHL. We now need to determine if it has similar efficacy in humans. This prospective study is a randomized, double-blind, placebo-controlled Phase 3 clinical trial of oral D-met to reduce noise-induced hearing loss (NIHL) and tinnitus. The goal of the study is to develop a safe, oral pharmacological agent to augment physical hearing protectors for noise exposures that exceed the protective capabilities of ear plugs and/or muffs. The study population is a cohort of Drill Sergeant (DS) instructor trainees during and 22 days after their 11 day weapons training. The primary objective of this study is to determine the efficacy of D-Met in preventing NIHL or reducing tinnitus secondary to a minimum of 500 rounds of M-16 weapons training occurring over an 11 day period..

15. SUBJECT TERMS
None provided

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
U		U		12	

Table of Contents

INTRODUCTION:

The purpose of this Phase 3 clinical trial is to determine if an oral, orange flavored suspension of D-methionine can prevent noise-induced hearing loss (NIHL) and tinnitus in our troops.

Hypotheses**:**
Primary Hypothesis**:** Administration of oral D-methionine prior to and during weapons training will reduce or prevent permanent NIHL.
Secondary Hypothesis**:** Administration of oral D-methionine prior to and during weapons training will reduce or prevent noise-induced tinnitus.
Primary outcome to test the primary hypothesis**:** Pure tone air-conduction thresholds.
Primary outcome to test the secondary hypothesis**:** Tinnitus questionnaires.

Specific Aims**:**

1. To determine whether administering oral D-methionine (D-met) can prevent permanent NIHL after weapons training. This aim will be addressed by comparing the results of D-met versus placebo administration starting 3 days prior to, during the 11 day period of weapons training (Monday-Friday of week 1 and Monday-Thursday of week 2), and 4 days after for a total of 18 days. Pure tone hearing thresholds will be assessed before and 19-22 days after completion of weapons training (i.e., 15-18 days after the last day of study drug/placebo administration).

2. To determine whether administering oral D-met can prevent tinnitus after weapons training. This aim will be addressed by comparing the results of D-met versus placebo administration starting 3 days prior to, during the 11 day period of weapons training (Monday-Friday of week 1 and Monday-Thursday of week 2) and 4 days after for a total of 18 days. Tinnitus questionnaires will be assessed before and 19-22 days after completion of weapons training (i.e., 15-18 days after the last day of study drug/placebo administration).

3. To monitor for any potential side effects of D-met in human subjects. This aim will be accomplished by subject query on each day of drug administration with routing of any adverse event reports to study medical personnel, statisticians and to the Food and Drug Administration (FDA).

Primary Endpoints

1) Primary endpoint is to confirm safety and tolerability of up to 100 mg/kg daily given in divided doses 12 hours apart.
2) Primary efficacy endpoint is change from baseline in pure-tone threshold as measured by absolute change and frequency of significant noise-induced threshold shift (STS)...
3) Secondary efficacy endpoint is change from baseline scores for the tinnitus scales for both loudness and annoyance.

Study Design**:**
This prospective study is a randomized, double-blind, placebo-controlled Phase 3 clinical trial of oral D-met to reduce NIHL and tinnitus. The goal of the study is to develop a safe oral pharmacologic agent to augment physical hearing protectors for noise exposures that exceed the protective capabilities of ear plugs and/or muffs. The study population is a cohort of Drill Sergeant (DS) instructor trainees during and 21 days after their 11 days of weapons training. The primary objective of this study is to determine the efficacy of D-Met in preventing or reducing NIHL and tinnitus secondary to a minimum of 500 rounds of M-16 weapons training occurring over a 2 week period. A total of 600 Drill Sergeant Instructor Trainees will be enrolled in the study and randomized to study drug or placebo for a final study cohort of 504 subjects. Subjects will be recruited during the first week of training. Participation will consist of an on-site Screening visit followed by a Baseline visit (Study Visit 1), an, and an End of Study visit (Study Visit 3), for a total of 3 Study Visits for each subject. Compliance and adverse event checks will be performed daily throughout the drug administration period. Subjects will be prescreened to review inclusion/exclusion criteria and medical history. Baseline and final audiologic testing will include otoscopy, tympanometry, and pure-tone hearing threshold testing at .5, 1, 2, 3, 4, 6, 8 kHz bilaterally. Tinnitus will be measured using standardized tinnitus assessment questionnaires. Subjects will take either the oral study drug or flavor matched placebo twice per day for 18 days starting 3 days prior to the weapons training, during the weapons training period and for an additional 4 days. Data will be independently analyzed through the Yale Occupational and Environmental Medicine Program. Data will be analyzed to determine 1) if there is a significantly reduced change in hearing threshold in the average of both ears for the D-met group as compared to the placebo group at the tested audiometric frequencies, 2) to determine if there is a significantly lower rate of significant threshold shift (STS) according to the Defense Occupational Environmental Health Readiness System- Hearing Conservation (DOEHRSHC) in either ear for the D-met group as compared to the placebo group 3) to determine if there is a significant difference in reported level of tinnitus between the D-met and the placebo groups and 4) to detect, report and analyze any side effects. This study is a collaboration among Southern Illinois University School of Medicine, the U.S. Army, and Yale University. The study includes a regulatory consultant to ensure full compliance with all regulatory agencies, committees, and boards. It is hoped that this study will move us forward in preventing NIHL and tinnitus world-wide.

Relevance: This study will test the hypotheses that oral D-met can prevent or significantly reduce permanent NIHL and potentially tinnitus in US military troops during weapons training in a cohort of experienced soldiers.

BODY:

The original Statement of Work (SOW) outlined several tasks to be completed before data collection could begin. We have completed and submitted all appropriate documents, received appropriate regulatory approvals and have successfully begun data collection. In addition, the study drugs have been successfully reformulated, undergone stability testing

and are currently being shipment to the testing site upon request. The following is a list of each SOW task and the current status of each:

SOW Task 1: First Quarter (Year 1): *To submit a complete Investigational New Drug (IND) Application to the FDA***:**

Task Completed: We received FDA 30-day safety review on May 2012.

SOW Task 2: First Quarter (Year 1): *To submit a completed Institutional Review Board (IRB) application***:**

Task Completed: We received initial formal DDEAMC IRB approval on November 28, 2012. However, we continue to make additions, revisions and resubmissions as needed.

SOW Task 3: First Quarter (Year 1) *To complete the Hiring of Study Staff and finalize corporate contracts*

(Year 1) SOW Task 3: *To complete the Hiring of Study Staff and finalize corporate contracts*

a. Yale Occupational Environmental Medicine Program: Task nearly completed. The original subcontract for Yale was signed and finalized. However, we are currently renegotiating the amount of programmer time because the data entry for the study was moved to Ft. Jackson. Therefore we wish to reduce the amount of programmer time at Ft. Jackson to supplement the time of the clinical coordinators at Ft. Jackson because they are now performing the data entry task. The revised Subcontract for Yale is currently undergoing finalization.

b. Ft. Jackson: Task nearly completed. Although both on-site study coordinators, Beth Bullock, R.N. and Shelley Laird, LPN, are in place and have been successfully recruiting and enrolling subjects, we are currently seeking an additional part time study assistant to help maintain full coverage at all times, particularly for weekend coverage. In addition, we have also begun a search for a part time civilian audiologist to assist in maintaining audiological coverage at all times due to the expected reassignment of CPT Bailey and the temporary three month absence of CPT Ludwig from the study.

c. SIUSOM/: SIU Center for Clinical Research: Tasked completed. All study personnel have been recruited, trained and are currently working on different aspects of the project.

d. KP Pharmaceuticals: Task nearly completed. We are near finalization of the revised subcontract with KP Pharmaceutical Technology for the drug reformulation. However the placebo and drug supply for the study are continuing during these negotiations.

e. Judi Weissinger, PhD: Task completed. The contract for Dr. Weissinger, is finalized and in force.

f. Colleen Le Prell, PhD: Task completed. Dr. Le Prell's consulting contract has been re-budgeted to reflect her significant decrease in active participation in the project**.** The funding for Dr. Le Prell was re-budgeted to Dr. Weissinger for the work in obtaining FDA approval for this clinical trial as a Phase 3 study rather than as originally planned as a Phase 2 study.

SOW Task 4: First Quarter (Year 1) *To complete study Site Visits*

a. Dr. Campbell has traveled to the study site on two occasions to finalize the study protocol/logistics and met with site leadership/study personnel. The initial visit was made on **December 11-13, 2011**. Due to significant changes in personnel at Ft Jackson, a subsequent site visit was made on **October 3-5, 2012** to orient new personnel to the study protocol.

b. An on-site visit and audit of KP Pharmaceuticals was made by Dr. Kathy Campbell in **May, 2012**.

c. The study team, comprising Dr. Campbell and Dr. Milbrandt, including Dr. Puczynski (SIU CCR Director), traveled to the study site on **August 7-8, 2012**. The study team met with key personnel representing most of the divisions which will be actively involved in study related activities including LTC Ludwig (Audiology), COL Mark Hidgon (Commander of MACH), and LTC Neil Page (PI and Chief of Clinical Services). The study team toured the facilities and was able to determine a new location at the DSS in which to install 2 new sound booths for study related audiological testing. The study team also met with MAJ Ochoa, the pharmacist from MACH, and worked out study drug related issues. The team also toured the DSS training center and met with the DSS Command and received updates/modifications on the DSS training schedule. The site visit proved successful in refining the study protocol and in establishing better interpersonal relations between the SIU and Ft Jackson study teams.

d. Dr. Anderson, SIU study coordinator, traveled to the study site on **October 10-13, 2012** to upload study documents into the DDEAMC IRBNet because SIUSOM does not have access through Army Knowledge Online (AKO).

e. A site initiation visit with the entire SIUSOM study team was completed on **August 26-29, 2013**.

f. The initial Site Monitoring Visit was completed on **Dec 10-11** by the study monitor, Dr. Joseph Milbrandt and his assistant Julie Bullard, R.N.

g. The second interim monitoring visit by Dr. Milbrandt is scheduled for the first week of **May 2014**.

SOW Task 5: Third Quarter: (Year 1): *To complete all necessary study documents.*

Task completed. All study documents were approved by the DDEAMC IRB on June 13, 2013. Minor additions and revisions will be completed and submitted as needed. The Manual of Operations has been finalized.

All electronic data capture documents through the Yale Research Electronic Data Capture (REDCap) are finalized and successfully operational.

SOW Task 6: *To recruit subjects for first pilot data.*

Task completed. The first of two groups of pilot subjects were recruited and enrolled on October 7, 2013 and October 10, 2013. The total number of participants completing the pilot study was nine.

.

SOW Task 7: *Send pilot data sent to Yale for data checking*

Task completed. All pilot data were successfully transmitted to Yale through the Research Electronic Data Capture (REDCap) system**.**

SOW Task 8: *To continue enrollment and recruitment with new classes starting every 2-3 weeks*

This task is ongoing. The projected enrollment to date was 120 subjects. Unfortunately, we were forced to withdraw 12 consented participants from DSS class 502-14 and did not attempt to recruit from class 503-14 due to the lack of available study drug during that time period. To date, 44 participants have been enrolled in the study, 9 participants have completed the study, 4 are in progress (have not yet had their final hearing test) and 7 are still in treatment (dosing).

The next recruitment briefings are schedule for:

07-April-2014, 21-April-2014, 05-May-2014, 19-May-2014, 23-June-2014

.

KEY RESEARCH ACCOMPLISHMENTS:

- Corporate contract renewals are near finalization (Yale and KP)
- We have begun our personnel search for additional civilian audiology study coverage
- Study drug and placebo have been re-formulated, tested and are currently shipping to the study site upon request

- The initial study monitoring visit by Dr. Joseph Milbrandt was made on Dec 10-11, 2013
- COL Mark Packer, M.D. was successfully recruited as medical monitor replacing Leonard Rybak, M.D. Dr. Rybak was replaced as independent medical monitor to avoid a conflict of interest secondary to his co-inventorship on a competing patent.
- The DSMC was successfully created and initially assembled on March 21, 2014

REPORTABLE OUTCOMES:
To date, no reportable outcomes are yet available because the clinical trial has not yet been completed.

CONCLUSION:
Excellent progress has been made regarding the start-up issues during the second 12 months of the grant period. The on-site team finalized our Manual of Operations. With the supplemental funding received from the DoD, we were able to provide the funds necessary for the reformulation of the study drug and do not anticipate any additional delays related to this issue. Although our enrollment numbers are less than expected at this point, we are currently exploring creative ways to increase those numbers. In addition, revised subcontracts with both KP Pharmaceutical Technology and Yale University are near final. Both the Master CRADA and SOW are now fully executed.

Immediate Future Plans:

- Dr. Milbrandt will make his second interim monitoring site visit the first week of May, 2014
- We will explore the possibility of hiring both a part time civilian study assistant and audiologist to ensure full study coverage at all times.
- We will explore and implement new ways to increase study enrollment
- We will continue to recruit and enroll study subjects
- We will continue to recruit additional ombudsmen as needed
- The on-site study coordinators will conduct at least one briefing for new Drill SGT Leaders

Overall, we are very appreciative of the number of individuals in the US Army in research administration and at Ft. Jackson and at Yale, the University of Florida, KP Pharmaceuticals, SIUSOM legal (counsel), clinical trials and grants offices, and our consultants that have been willing to patiently work with us on performing the extra work required for this collaboration to successfully move forward. We are all fully committed to preventing noise-induced hearing loss and tinnitus in our troops. We are very grateful for this opportunity.

REFERENCES: N/A